Continuous Intravenous Insulin Infusion Reduces the Incidence of Deep Sternal Wound Infection in Diabetic Patients After Cardiac Surgical Procedures

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Background. **Diabetes mellitus is a risk factor for deep sternal wound infection after open heart surgical procedures. We previously showed that elevated postoperative blood glucose levels are a predictor of deep sternal wound infection in diabetic patients. Therefore, we hypothesized that aggressive intravenous pharmacologic control of postoperative blood glucose levels would reduce the incidence of deep sternal wound infection.**

Methods. **In a prospective study of 2,467 consecutive diabetic patients who underwent open heart surgical procedures between 1987 and 1997, perioperative blood glucose levels were recorded every 1 to 2 hours. Patients were classified into two sequential groups: the control group included 968 patients treated with sliding-scale–guided intermittent subcutaneous insulin injections (SQI); the study group included 1,499 patients treated with a continuous intravenous insulin infusion in an attempt to maintain a blood glucose level of less than 200 mg/dL. There were no differences between these groups with respect to age, sex, procedure, bypass time, antibiotic prophylaxis, or skin preparation methods.**

Results. **Compared with subcutaneous insulin injections, continuous intravenous insulin infusion induced a significant reduction in perioperative blood glucose levels, which led to a significant reduction in the incidence of deep sternal wound infection in the continuous intravenous insulin infusion group (0.8% [12 of 1,499]) versus the intermittent subcutaneous insulin injection group (2.0% [19 of 968], $p = 0.01$ by the χ^2 test). Multivariate logistic regression revealed that continuous intravenous insulin infusion induced a significant decrease in the risk of deep sternal wound infection ($p = 0.005$; relative risk, 0.34), whereas obesity ($p < 0.03$; relative risk, 1.06) and use of an internal thoracic artery pedicle ($p = 0.1$; relative risk, 2.0) increased the risk of deep sternal wound infection.**

Conclusions. **Use of perioperative continuous intravenous insulin infusion in diabetic patients undergoing open heart surgical procedures significantly reduces major infectious morbidity and its associated socioeconomic costs.**

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Median sternotomy has long been an ideal incision for cardiac surgical procedures, affording the surgeon excellent exposure even in the most difficult of cases. However, deep sternal wound infection (DSWI) after midline sternotomy is one of the most devastating complications subsequent to cardiac operation. Diabetic patients are particularly prone to this complication. The purpose of the present report was to validate a management protocol for diabetic patients that would profoundly decrease this risk.

Despite recent advances in the prevention of the long-term sequelae of diabetes mellitus [1], reduction of acute infectious problems related to surgical trauma in the diabetic patient has been elusive. Diabetes mellitus has been established as an independent risk factor for postoperative surgical wound infection [2–4], with infection rates two to five times more prevalent than in the nondiabetic population [5]. Poststernotomy mediastinitis in diabetic patients after open heart surgical procedures increases operative mortality twofold to threefold [6].

It has been shown that intensive treatment of hyperglycemia in insulin-dependent diabetic patients effectively reduces the incidence of long-term complications [1]. There is a growing body of clinical and experimental evidence that hyperglycemia increases the risk of nosocomial infections and may actually be a causal factor in the development of these infections in critically ill patients [7].

This rationale led us to first investigate the relation between postoperative hyperglycemia and DSWI [6]. In that study we revealed that elevated blood glucose levels (> 200 mg/dL) on the first and second postoperative days (PODs) in diabetic patients are associated with a higher

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incidence of DSWI. In fact, the average blood glucose level over these 2 days was found to be the strongest predictor of any DSWI in a diabetic patient who has undergone an open heart surgical procedure. We therefore hypothesized that a continuous intravenous insulin infusion (CII) in the perioperative period would substantially reduce the incidence of hyperglycemia and therefore significantly lower the rate of DSWI in diabetic patients.

Material and Methods

Patients

All known diabetic patients consecutively admitted to Portland St Vincent Medical Center for open heart surgical procedures between January 1987 and November 1997 were entered into the study (n = 2,467). Historical, demographic, and surgical variables that might possibly be associated with infectious complications were collected in a common database. These variables included age, sex, height, weight, race, type of preoperative diabetic control (insulin, oral, diet, or none), steroid use, smoking history, recent weight loss less than 15%, concurrent infection, admission leukocyte count, historical comorbidities (hypertension, congestive heart failure, renal failure, renal insufficiency, peripheral vascular disease), Society of Thoracic Surgeons operative status (elective, urgent, emergent, salvage), redo or first-time cardiac procedure, type of procedure, bypass time (as a finite indicator of overall operative time), units of blood transfused, prolonged (> 48 hours) intubation, inotropic use more than 48 hours, and length of hospital stay. Patients were then screened for postoperative infectious complications or readmission for same.

In the intraoperative and postoperative periods, the patients' blood glucose levels were prospectively monitored with Accu-check Easy (Boehringer Mannheim, Indianapolis, IN) every 1 to 2 hours through fingerstick or arterial line drop sample and recorded. For purposes of data analysis, daily mean blood glucose levels were then calculated by averaging all glucose levels obtained clinically during the day of operation and each of the first through fifth PODs.

Study Groups

Patients were classified into two sequential groups to maintain tight diabetic protocol compliance within each group. The control group, which included 968 patients operated on between January 1, 1987, and September 1, 1991, received individualized sliding-scale–guided subcutaneous insulin injections (SQI) as a method of postoperative glucose regulation. Treatment was administered every 4 hours, with the goal of keeping blood sugar levels at or below the "safe" limit of 200 mg/dL.

The study group included diabetic patients who underwent open heart surgical procedures between September 1, 1991, and November 30, 1997 (n = 1,499). Blood sugar levels in this group were manipulated by means of a CII. The insulin drip was titrated on the basis of the most recent fingerstick glucose measurement to maintain blood glucose levels between 150 and 200 mg/dL. A standardized protocol was developed so that it could be instituted and administered entirely by the nursing staff in all postoperative diabetic patients. The Portland CII protocol (Appendix) consists of a starting intravenous insulin infusion dosage, blood glucose testing frequency requirements, insulin infusion titration, and cessation orders. The CII protocol was automatically ordered by the surgeons and was administered entirely by the critical care and telemetry floor nursing staff without physician intervention.

Surgical infection prophylaxis remained constant through the entire study period, and all procedures were performed by the same surgical team. All patients were monitored closely for infectious complications, and all charts were reviewed for any subsequent admissions for infection.

Classification of Infectious Complications

DEEP STERNAL WOUND INFECTION. Chest wound infections involving the sternum or mediastinal tissues, including mediastinitis, were classified as DSWI.

SUPERFICIAL STERNAL WOUND INFECTION. Chest wound infections involving the skin or subcutaneous tissues, or both, were classified as superficial sternal wound infection, not involving the sternal bone or wires.

Other Definitions

DIABETIC PATIENT. A diabetic patient was defined as one who experienced chronic glucose intolerance, either insulin dependent or non–insulin dependent, at the time of operation. Patients who did not carry the preoperative diagnosis of diabetes but who temporarily required insulin in the postoperative period relative to the administration of total parental nutrition or inotropes (eg, epinephrine) and did not have glucose intolerance after the cessation of these modalities were not included in the study.

BODY MASS INDEX. Body mass index was calculated as weight (kg) divided by height (m^2) [8].

Biostatistical Methods

Data variables were analyzed using SPSS (Chicago, IL) statistical software. Results are reported as mean ± standard error of the mean, where appropriate. Univariate analysis was performed using χ^2 tests for categoric variables, t tests for continuous variables, and the F test to compare variance. Forward stepwise multivariable logistic regression was used to test the independent association of multiple variables against DSWI. Multivariable results are given with 95% confidence intervals.

Results

Demographics

Between January 1987 and November 1997, 14,468 patients underwent open heart surgical procedures through

Table 1. Demographic and Perioperative Comparison of Intermittent Subcutaneous Insulin Control Group and Continuous Intravenous Insulin Infusion Study Group

Variable	SQI Group	CII Group	*p* Value
Preoperative			
Age (y)	65	65	0.9
Male (%)	62	60	0.4
Diabetic control (%)			0.8
Insulin dependent	35	36	
Oral agent	49	48	
Diet only	10	10	
None	6	6	
Smoking (%)	26	26	0.9
Hypertension (%)	54	67	0.0001
Congestive heart failure (%)	28	23	0.01
Renal failure (%)	6.2	5.9	0.7
Renal insufficiency (%)	3.4	6.6	0.001
Peripheral vascular disease (%)	14	15	0.6
Body mass index (kg/m^2)	28.4	29.6	0.0001
Weight loss >15% (%)	8	11	0.08
Admission glucose (mg/dL)	194	192	0.5
Admission WBC (10^3/mL)	8.8	8.8	0.9
Steroid use (%)	1.9	3.5	0.03
Perioperative			
Redo sternotomy (%)	13	13	1.0
Urgent/emergent status (%)	51	75	0.0001
Procedure (%)			0.8
CABG	87	85	
Valve	7	6	
Valve/CABG	5	8	
Other	1	1	
Internal thoracic artery/CABG (%)	64	71	<0.001
Cardiopulmonary bypass time (min)	90	89	0.7
Transfused PRBC (units)	2.2	1.6	0.0001
Inotropes >48 h (%)	14	10	0.004
Ventilation >48 h (%)	8	8	1.0
Length of stay (days)	10.7	8.5	0.0001
Subsequent mortality (%)	6.1%	3.0%	0.03

CABG = coronary artery bypass grafting; CII = continuous intravenous insulin infusion; PRBC = packed red blood cells; SQI = subcutaneous insulin; WBC = white blood count.

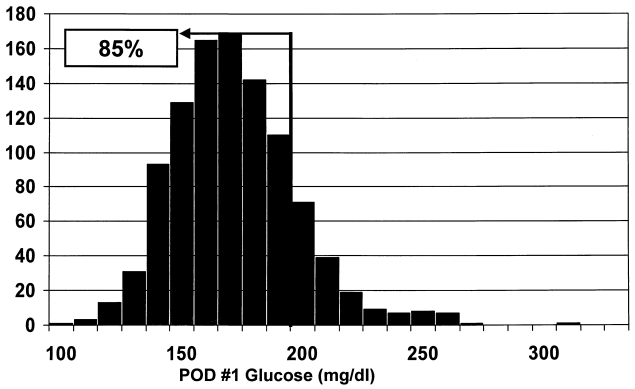
median sternotomy at St Vincent Medical Center. Seventeen percent of these patients (n = 2,467) were classified as diabetic at the time of admission, and all were enrolled in the study. Mean age was 65 ± 10 years, and 62% of patients were men. The cardiac procedures performed in this diabetic cohort included coronary artery bypass grafting in 2,117 patients, valve replacements in 158, combined valve/bypass grafting procedures in 167, and other open heart procedures in 25. At least one internal thoracic artery (ITA) was used in 1,446 (68%) of the 2,117 bypass grafting procedures. Bilateral ITAs were used in 9 patients.

Insulin-dependent diabetic patients comprised 36% of the group; diabetes was controlled by oral agents on admission in 48% and by diabetic diet only in 10%; 6% had no diabetic glucose control on admission.

Demographic and perioperative comparisons of the SQI control group and the CII study group are shown in Table 1. There were no significant differences with respect to age, sex, procedures performed, redo sternotomies, cardiopulmonary bypass time, or transfusions. The CII group had a significantly higher prevalence of hypertension, renal insufficiency, obesity, steroid usage, and greater use of ITA grafts in patients undergoing bypass grafting. The SQI group had higher prevalence of congestive heart failure, prolonged inotropic support, more transfusions, and a longer length of postoperative stay.

Infectious Complications

Deep sternal wound infection occurred in 31 of the 2,467 diabetic patients (1.3% overall). Seventy-four percent (23 of 31) of DSWI occurred after initial discharge and thus required a second admission. The culprit infectious organism was Gram stain positive in 22 patients, Gram stain negative in 6, and unknown in 3. There were no anaerobic, fungal, or yeast infections. Superficial sternal



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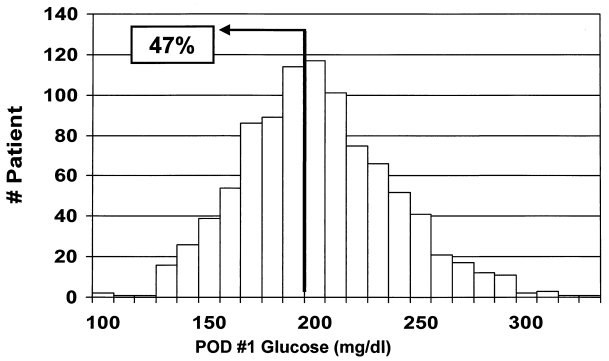

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Fig 1. Distribution curves of mean glucose levels on POD 1 in patients in the CII study group (A) *and control (SQI) group* (B). Vertical line *represents the desired goal of 200 mg/dL. Tighter glucose control with CII is reflected by the fact that 85% of the CII study group successfully achieved levels below 200 mg/dL. In the SQI control group, in contrast, there is only a 47% compliance with target levels.*

wound infections occurred in 16 (0.6%) of 2,467 patients. Deep donor site infections occurred in 14 (0.6%) of 2,467 patients and superficial donor site infections in 16 (0.6%) of 2,467.

Glucose Control

Direct comparison of the daily mean blood glucose levels between the SQI and CII groups reflects markedly improved postoperative glucose control in the CII group. Mean blood glucose levels on the day of operation through the third POD were significantly lower within the CII group than in the SQI control group (199 ± 1.4 versus 241 ± 1.9 mg/dL on the day of operation, 176 ± 0.8 versus 206 ± 1.2 mg/dL on POD 1, 181 ± 1.2 versus 195 ± 1.3 mg/dL on POD 2, and 179 ± 1.5 versus 188 ± 1.4 mg/dL on POD 3, CII group versus SQI group, respectively; $p < 0.0001$ for all comparisons). The aggressive CII approach resulted in overall tighter glucose control as well, with less daily variance, as evidenced by the smaller standard deviation in the CII group (standard deviation, 36 mg/dL for SQI on POD 1 versus standard deviation, 26 mg/dL for CII on POD 1, $p < 0.001$). The achievement of strict glucose control with the aggressive CII method is exemplified in Figures 1A and 1B, which are distribution curves of the average blood glucose level for each patient in the CII and SQI groups on POD 1.

Comparison of the mean blood glucose levels between patients with DSWI and those without DSWI is shown in Figure 2. Glucose levels on POD 1 were 190 ± 1 mg/dL in patients without DSWI and 209 ± 7 mg/dL in patients with DSWI ($p = 0.02$). Glucose levels on POD 2 were 188 ± 1 mg/dL in patients without DSWI and 206 ± 8 mg/dL in patients with DSWI ($p = 0.01$).

Implementation of the CII protocol resulted in a 2.5-fold decrease in the rate of DSWI compared with that for SQI. The rate of DSWI dropped from 1.9% (19 of 968) with SQI to 0.8% (12 of 1,499) with CII (χ^2 test, $p = 0.011$).

Univariate Analysis of Deep Sternal Wound Infection

Multiple variables were considered in addition to method of glucose control (SQI or CII) as possible predictors of DSWI. Univariate statistical analysis was carried out for each variable in relation to DSWI and is shown in Table 2.

Multivariate Analysis of Deep Sternal Wound Infection

All univariate variables that were suggestive of a possible association with DSWI were entered into a forward stepwise multivariable logistic regression analysis. Variables with little to no predictive significance ($p > 0.5$) after each run were eliminated to obtain a cleaner predictive model. The final multivariate model run in a nonstepwise fashion (n = 2,353) (Table 3) revealed that CII ($p = 0.005$; relative risk, 0.34) produced a significant decrease in the risk of DSWI. Obesity, as measured by body mass index, increased the risk of DSWI ($p = 0.03$; relative risk, 1.06), as did the use of an ITA pedicle ($p = 0.1$; relative risk, 2.0).

Comment

The present study reconfirms our previous finding [6] that hyperglycemia in the first 2 PODs is significantly associated with, and is an independent predictor of, DSWI (Table 4). These data indicate that hyperglycemia after cardiac operation in the diabetic patient may actu-

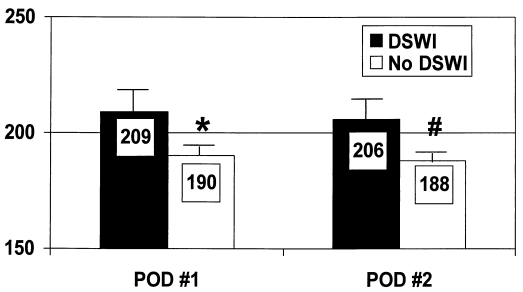

Fig 2. Daily comparison of mean blood glucose levels between patients with DSWI and those without DSWI (No DSWI). (*p = *0.02;* #p = *0.01.)*

Table 2. Univariate Analysis of Deep Sternal Wound Infection

Variable	No DSWI	DSWI	*p* Value
Preoperative			
Age (y)	65	62	0.09
Male (%)	62	58	0.7
IDDM (%)	36	52	0.07
Smoking (%)	15	23	0.2
Body mass index (kg/m^2)	29.2	30.9	0.2
Weight loss >15% (%)	10	12	0.7
Admission WBC (10^3/ml)	8.9	9.5	0.1
Steroid use (%)	3	0	0.3
Hypertension (%)	61	55	0.4
Congestive heart failure (%)	26	37	0.2
Renal failure (%)	6	10	0.4
Renal insufficiency (%)	5	0	0.2
Peripheral vascular disease (%)	15	23	0.2
Perioperative			
Redo sternotomy (%)	14	7	0.2
Urgent/emergent status (%)	64	55	0.7
Procedure (%)			0.9
CABG	86	84	
Valve	6	6	
Valve/CABG	7	10	
Other	1	0	
Internal thoracic artery (%)	68	85	0.07
Cardiopulmonary bypass time (min)	90	90	1.0
Transfused PRBC (units)	1.9	2.4	0.3
Inotropes >48 h (%)	12	7	0.3
Ventilation >48 h (%)	8	0	0.09
POD 1 blood glucose >200 mg/dL (%)	34	42	0.04
Length of stay (days)	9.5	25	<0.001
Mortality (%)	3.8	19	<0.001

CABG = coronary artery bypass graft; IDDM = insulin-dependent diabetes mellitus; POD = postoperative day; PRBC = packed red blood cells; WBC = white blood count.

ally be a causal factor in that infectious process as well. When postoperative hyperglycemia was manipulated through an aggressive intravenous insulin infusion aimed at maintaining glucose levels in the 150 to 200-mg/dL range, the incidence of DSWI was significantly decreased. The use of the CII protocol was found to protect against DSWI, independently decreasing the risk of DSWI by approximately 66%. Obesity and the use of ITA grafts were shown to increase the risk of DSWI in diabetic patients by factors of 1.06 (per body mass unit) and 2, respectively.

The significant ($p = 0.01$) decrease in the observed rate of DSWI in the CII study group compared with the SQI control group occurred despite a skewed compositional bias against the CII group in terms of infectious risk.

Table 3. Multivariate Analysis of Deep Sternal Wound Infections in 2,353 Diabetic Patients With Regard to Continuous Intravenous Insulin Infusion[a]

		Relative Risk	
Variable	*p* Value	Point Estimate	95% Confidence Interval
CII protocol	0.005	0.34	0.14–0.74
Increasing BMI	0.03	1.06	1.00–1.12
ITA graft	0.1	2.0	0.86–4.34

[a] Multivariable analysis of deep sternal wound infection in diabetic patients with the study group (continuous intravenous insulin infusion [CII]) in the final equation.

BMI = body mass index; ITA = internal thoracic artery graft.

Table 4. Multivariable Analysis of Deep Sternal Wound Infections in 1,920 Diabetic Patients With Regard to Postoperative Glucose Level[a]

		Relative Risk	
Variable	*p* Value	Point Estimate	95% Confidence Interval
POD 1 glucose	0.002	1.01	1.01–1.02
Increasing BMI	0.06	1.06	1.0–1.12
ITA graft	0.02	2.3	1.01–3.3

[a] Multivariable analysis of deep sternal wound infection in diabetic patients with mean glucose on postoperative day (POD) 1 in the final equation; postoperative glucose level is a reciprocal surrogate for continuous intravenous insulin infusion therapy in this analysis.

BMI = body mass index; ITA = internal thoracic artery graft.

Specifically, the CII group was significantly ($p < 0.0001$) more obese (as measured by body mass index) and had a higher use of ITA conduits. Both of these variables have been shown to be independent predictors of DSWI in this and other studies [2, 4, 9]. In addition, the CII group had a significantly ($p = 0.03$) higher incidence of preoperative steroid use and a higher percentage of urgent/emergent cases, again increasing the bias against decreased DSWI [10]. These significant differences in the composition of the study and control groups should have negatively predisposed the CII group to a higher risk of DSWI.

The Portland CII protocol (Appendix) consists of (1) a starting intravenous insulin infusion dosage that is based on the first blood glucose measurement greater than 150 mg/dL; (2) blood glucose testing frequency requirements that are based on the stability of the insulin infusion rate and the status of concomitant vasopressor infusions; (3) insulin infusion titration orders that are based on the most recent blood glucose level; and (4) cessation orders that are based on adequate (<150 mg/dL) blood glucose control beyond the second POD and an active oral diet. This insulin infusion protocol is designed to rapidly achieve and maintain blood glucose levels in the range of 150 to 200 mg/dL. As levels fall below 150 mg/dL, the patient is weaned off continuous intravenous insulin infusion. The distribution curve of the first POD mean blood glucose level (Fig 1A) demonstrates that target hyperglycemia (>200 mg/dL) was eliminated in 85% of patients. In contrast, SQI control (Fig 1B) resulted in levels below 200 mg/dL only 47% of the time.

Implementation of the Portland CII protocol was staged to a specific point in time to achieve the highest compliance possible on the part of the nursing staff who administered the protocol. When the protocol was initiated, mean daily glucose measurements did not immediately step down to levels below 200 mg/dL. Rather, there was a cautious initial learning period of approximately 4 months during which the nursing staff gradually became more comfortable with the idea that a CII protocol in patients with glucose levels between 150 and 200 mg/dL was a safe mode of therapy. Were the CII protocol to be administered concomitantly alongside the SQI protocol, it is likely that we would not have rapidly achieved the tight daily control exemplified by the markedly decreased variances in daily mean glucose in the CII group.

The increasing temporal compliance with the CII protocol among the nursing staff eventually (1994) allowed continuation of the CII on the telemetry floor after transfer from the intensive care unit. As this transition occurred, the CII protocol became even more compatible with "fast-track" intensive care unit transfer programs. With ever-increasing postoperative nursing compliance with the CII, DSWI rates continued to fall. The trend of DSWI in diabetic patients at our institution has been significantly downward (slope, −0.52%/year; $p = 0.01$) since the institution of CII in 1991 (Fig 3). Since 1994, the annual incidence of DSWI in the diabetic population has not been statistically different from that in the nondiabetic population (0.3% for each, $p = 0.9$). Anecdotally, we

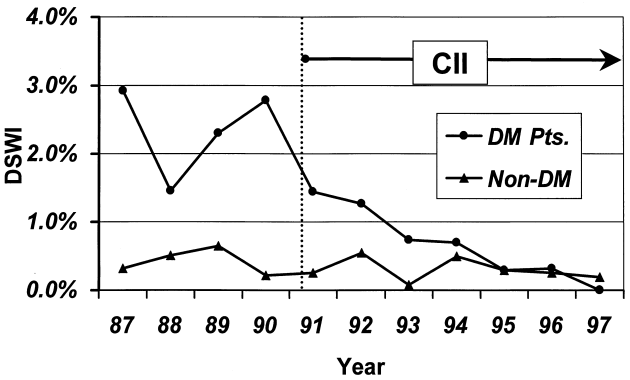

Fig 3. Annual rates of DSWI in diabetic and nondiabetic patients after cardiac surgical procedures at Providence St Vincent Medical Center from 1987 through 1997. Note the significant downward trend (slope, −0.52%/year, p = *0.03) since the implementation of the CII protocol. Diabetic DSWI rates since 1995 appear to have normalized to that of the nondiabetic population. (DM = diabetes mellitus; Pts. = patients.)*

have not experienced a single DSWI after cardiac operation in a diabetic patient since August 1996 (15 months, 494 patients).

During the same 11-year time frame of the study, the observed annual rate of DSWI in the nondiabetic patient population at St Vincent Medical Center has remained relatively constant at 0.3% (40 of 12,001; slope, −0.02%/year; $p = 0.3$). Prophylaxis for surgical infection in nondiabetic patients was the same as that for diabetic patients. Standard prophylaxis was unchanged through the entire study period and included a second-generation cephalosporin (cefamandole or cefuroxime) for perioperative antibiosis; a 2% iodine tincture followed by an isopropyl alcohol rinse; Ioban 2 iodophor–impregnated steridrape (3M Healthcare, St Paul MN); and neomycin/polymixin B sulfate solution (Schein Pharmaceutical, Floorham Park, NJ) sponge scrub of the subcutaneous tissues at the completion of sternal closure. Bone wax use is avoided or kept to a minimum. There were no changes, other than the change from SQI to CII in diabetic patients in September 1991, in the perioperative or operative protocols during the entire period of this study.

The CII protocol is not infallible, and diabetic patients remain at risk for DSWI, subject to proper implementation and other risk factors. In our last diabetic patient with DSWI (August 1996), the CII protocol was not aggressively implemented because of surgeon preference, and the patient retained elevated glucose levels of 240, 259, and 241 mg/dL on PODs 0, 1, and 2, respectively. Even in the setting of excellent glucose control, there are still patients who develop infections, indicating that hyperglycemia is not the only causal factor for DSWI.

Other multivariate studies of DSWI have identified several risk factors for DSWI, including obesity [2, 4, 9], diabetes [2–4, 9, 10], single [3] and bilateral ITA grafts [3, 11], steroid use [10], chronic obstructive pulmonary disease [12], prolonged ventilation [13], smoking [9], male sex [12], duration of cardiopulmonary bypass and aortic

cross-clamp time [3], and positive nasal *staphylococcus aureus* cultures [14]. Obesity (relative risk range, 2.0 to 3.8) and diabetes (relative risk range, 2.6 to 3.8) are the risks most often cited [4, 9], with ITA grafting a close third.

The current study suggests that hyperglycemia on the first and second POD remains the single most important predictor of DSWI in the postoperative diabetic population. When the multivariate analysis was run with the mean blood glucose level from POD 1 in the variable mix, it replaced CII in the equation (Table 4) ($p = 0.002$; relative risk, 1.014). Essentially, CII and hyperglycemia are reciprocal surrogates for DSWI risk—hyperglycemia markedly increases the risk, whereas the CII protocol, through the direct elimination of hyperglycemia, reduces the risk. To date, there has been no multivariate study of DSWI risk in the diabetic population alone other than our previous work. Our studies of DSWI have centered on this high-risk subpopulation of patients undergoing open heart surgical procedures and the relation between hyperglycemia and infection in this group [6].

Interestingly, as our surgical team came to fully appreciate the benefits of CII in preventing hyperglycemia and in normalizing the subsequent risk of DSWI in diabetic patients, we became more aggressive in expanding the armamentarium of treatment options for diabetic patients with coronary artery disease. In the past 3 years, bilateral ITA grafts have been used in 9 diabetic patients, without a single episode of DSWI. In the CII study group we have seen an increasing incidence in ITA use and obesity in the setting of a decreasing annual incidence of DSWI. This combination has altered the multivariable analysis of DSWI risk over time as more patients were entered into the study. The use of a single or bilateral ITA pedicle was significant ($p = 0.02$, 98% confidence of significance) when we first analyzed these data in 1995 [6]. However, this important variable has lost significance over time ($p = 0.1$, 90% confidence of significance) as a consequence of higher use of ITA grafts in diabetic patients without subsequent occurrences of DSWI.

Internal thoracic artery dissection causes temporary sternal ischemia, which may predispose to DSWI. The degree of temporary sternal ischemia is nearly doubled by the use of bilateral ITA grafts [15]. Reported rates of DSWI in diabetic patients who undergo bilateral ITA grafting are as high as 12% to 17% [3, 16]. It may well be that hyperglycemia in the setting of a devascularized sternum leads to a synergistic milieu that culminates in an unacceptable rate of DSWI in diabetic patients with bilateral ITA grafts. These studies led most cardiothoracic surgeons to believe that bilateral ITA grafts in diabetic patients were to be strictly avoided. Our experience, although not conclusively proving so, suggests that institution of the Portland CII protocol may obviate the infectious risk of bilateral ITA grafts in the diabetic patient population through the elimination of significant postoperative hyperglycemia.

Why, then, is hyperglycemia such a potent risk factor for DSWI? There is a growing body of clinical and experimental evidence that hyperglycemia impedes the normal physiologic responses to infection. In vitro and in vivo studies have shown that periods of hyperglycemia are associated with accelerated nonenzymatic glycosylation of body proteins, or the nonenzymatic addition of sugar molecules to the exposed lysine residues on extracellular proteins [17, 18]. Short-term glycosylation of immunoglobulin causes its inactivation [18]. Glycosylation of the C3 component of complement occurs at its opsonic binding site and renders it impotent, unable to bind to the surface of invading bacteria [19]. In addition, Hennessey and colleagues [17] have shown that glycosylation of newly synthesized collagen in hyperglycemic animals is associated with increased collagenase activity and decreased wound collagen content. The resultant wound healing impairment improves dramatically with control of glucose concentrations [17].

Several abnormalities in leukocyte function have also been identified that are caused by the hyperglycemic state. These include abnormalities in granulocyte adherence [20, 21], impaired phagocytosis [22], delayed chemotaxis [23], and depressed bacteriocidal capacity [22, 24]. The degree of hyperglycemia that has been shown to impair phagocytic function, either in vitro or in clinical trials, is as low as 11.1 mmol/L (200 mg/dL) [7]. Most interestingly, these leukocyte deficiencies appear to improve with aggressive glycemic control [25]. This correlation is further substantiated by reports that the degree of phagocytic impairment varies directly with glucose levels [26] and can be reversed with control of plasma glucose [27].

The major weakness of the present study is its temporal sequential nature. We recognize that there have been subtle cumulative improvements in all areas of open heart surgical intervention over the past 11 years, which may play a role in both the diminution of mortality and DSWI seen during the course of this study. Nonetheless, the reduction of hyperglycemia through the use of a CII protocol is a safe and cost-effective mode of postoperative diabetic therapy. This therapy is easy to administer, takes less nursing time than SQI, is less invasive to the postoperative patient, and has the added potential of effecting improved outcomes.

The socioeconomic costs of DSWI are staggering. A single DSWI in our institution during the present study generated an average of $26,400 in additional charges and increased the average length of stay by 16 days. These figures are comparable to those previously published [28]. Psychological morbidity from pain, suffering, and altered body image is immeasurable. The increase in mortality from DSWI is directly measurable at five times baseline (3.8% versus 19%). Assuming that most cardiac centers in this country use the sliding-scale SQI method of postoperative control as a standard, we can directly estimate the socioeconomic savings if the Portland CII protocol were to be implemented nationwide (Table 5). There were approximately 742,000 adult open heart procedures performed in the United States in 1995 [29]. If the prevalence of diabetes in the population undergoing cardiac surgical procedures is constant at 20% [3], then 148,400 diabetic patients underwent cardiac surgical intervention with nearly a 2% risk of developing DSWI

Table 5. Estimated Socioeconomic Outcomes and Projected Annual Savings in the United States With Use of Standardized Continuous Intravenous Insulin Infusion[a]

	SQI Group	CII Group	Savings
No. of DSWIs	2,968	1,009	1,959
Additional hospital days	47,488	16,146	31,342
Additional costs ($)	78,355,200	26,640,768	51,714,432
No. of deaths	564	192	372

[a] This projection assumes 742,000 annual cardiac operations [29], a 20% prevalence of diabetes in the cardiac surgical intervention population, a 2% incidence of deep sternal wound infections (DSWIs) in those treated with subcutaneous insulin, and a 20% mortality rate for diabetic patients with deep sternal wound infection; additional hospital days based on 16 extra days per patient with deep sternal wound infection; additional charges (in dollars) based on $26,400 per patient with deep sternal wound infection; decrease in deep sternal wound infection with continuous intravenous insulin (CII) based on relative risk of 0.34.

SQI = subcutaneous insulin mode of diabetic control.

(2,968 potential DSWIs). According to our multivariate analysis, the risk of developing DSWI in these patients could have been reduced by 66% (a relative risk of 0.34) through the use of the CII protocol, reducing the potential number of DSWIs to 1,009. Use of the CII protocol would have resulted in 1,959 fewer DSWIs, thus saving $51.7 million in hospital charges, 31,342 hospital days, and 372 patient lives.

In conclusion, the present study demonstrated that (1) hyperglycemia in the immediate postoperative period remains an independent predictor of and may be a causal factor in DSWI in diabetic patients; (2) postoperative hyperglycemia in diabetic patients may be safely and effectively managed through the institution of the Portland CII protocol; and (3) the incidence of DSWI in diabetic patients can be normalized to that of the nondiabetic population (Fig 3) through the use of a CII protocol that aims to aggressively eliminate postoperative hyperglycemia.

The present study further suggests that uncontrolled postoperative hyperglycemia in diabetic patients, not the diagnosis of diabetes itself, is the true risk factor for DSWI; that the use of bilateral ITA pedicled grafts in diabetic patients need not be avoided if hyperglycemia is controlled; and that the national socioeconomic costs of DSWI in diabetic patients are staggering and could potentially be reduced through the universal use of the Portland CII protocol for postoperative glucose control.

We extend our sincere appreciation to Steven Bookin, MD, endocrinologist, for writing a continuous intravenous insulin protocol that could be safely and effectively implemented by the nursing staff. Appreciation is extended to Patti Luckerath, Chris Pollack, and Elissa Walsh for assistance with data collection. We also thank Cindy Fessler and Natasha Lodahl for their tireless assistance in the preparation of the manuscript, figures, and slides.

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Appendix. Portland Protocol for Continuous Intravenous Insulin Infusion in Postoperative Diabetic Patients Undergoing Cardiac Surgical Procedures

1. Start insulin infusion through pump piggyback to maintenance intravenous infusion as follows: Test blood glucose level by fingerstick method or arterial line drop sample:

Blood Glucose (mg/dL)	Insulin (units/h)
<150	0
150–200	1
201–250	2
>251	3

2. Frequency of blood glucose testing:
   a. Every 1 hour until stable (when frequent changes in insulin dosage are no longer necessary, and glucose is in the range 150 to 200 mg/dL); then test every 2 hours.
   b. When weaning from vasopressors (eg, epinephrine), check every 30 minutes until stable.
   c. May stop testing every 2 hours on postoperative day 3 [see item 4].

3. Insulin titration:

Blood Glucose	Action
<75	Stop insulin; give 25 mL of 50% dextrose injection and recheck blood glucose in 30 min; when blood glucose is >150 mg/dL, restart with rate 50% of previous rate
75–100	Stop insulin; recheck blood glucose in 30 min, when blood glucose is >150 mg/dL, restart with rate 50% of previous rate
101–150	If <10% lower than last test, decrease rate by 0.5 units/h; if >10% lower than last test, decrease rate by 50%
151–200	Same rate
201–250	If lower than last test, use same rate; if higher than last test, increase rate by 0.5 units/h
>250	If >10% lower than last test, use same rate; if <10% lower than last test *or* if higher than last test, increase rate by 1 unit/h

   If blood glucose is >251 mg/dL and has not decreased after three hourly increases in insulin, then double insulin rate.

4. Start continuous intravenous insulin protocol during operation and continue postoperatively through the day of operation and the first and second postoperative days. Patients who are not receiving enteral nutrition on the third postoperative day should remain on this protocol until receiving at least a soft American Diabetes Association diet.

5. American Diabetes Association diabetic diet starts with any oral intake.

6. On the third postoperative day, restart preadmission glycemic control medications when patient is tolerating soft diet. If not tolerating soft diet, consult physician for new orders at that time.

7. For patients with previously undiagnosed diabetes mellitus and hyperglycemia: start Portland protocol if blood glucose is >200 mg/dL. Consult endocrinologist on postoperative 2 for diabetes 0mellitus workup and follow-up orders.

The Portland protocol for continuous intravenous insulin infusion in postoperative diabetic patients undergoing cardiac surgical procedures is available online at
www.starrwood.com/research/insulin.html

DISCUSSION

DR. ALFRED T. CULLIFORD III (New York, NY): Many fine papers presented before this Society address the treatment of postoperative complications. The treatment of deep sternal wound infections (DSWIs) is certainly no exception. This vexing problem has been treated by aggressive debridement, closed antibiotic irrigation, muscle flaps, myocutaneous advancement, omental transfer, and so on. This landmark study by Dr Furnary and his associates from Portland is unique and timely because it addresses prevention of this problem by continuous postoperative insulin infusion, maintaining glucose levels between 150 and 200 mg/dL.

Nearly 2,500 diabetic patients were studied, and during the past several years, 1,500 had glucose control below 200 mg/dL with continuous infusion. With this regimen, they noted a drop in DSWI rates from 1.9% to 0.8% and also observed, from the present report, a frequency of leg wound problems in only 1% of patients. This is a singular accomplishment and is particularly impressive because in the last 494 patients treated in 15 months, there was not a single instance of a DSWI.

I have three questions: (1) I note from your report that the internal thoracic artery (ITA) was used in 70% of patients in the bypass grafting group, with only a dozen or so of bilateral implants. Using these new management strategies, would you recommend routine use of one and perhaps both ITAs in otherwise healthy diabetic patients who do not have chronic obstructive pulmonary disease or overly obese? (2) What dose of insulin was used intraoperatively to achieve these glucose levels, and was hypoglycemia a significant postoperative problem, particularly as the nursing staff became familiar with the Portland protocol for continuous infusion? And finally, (3) nearly

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